Refer to: Cleaver T, Carretta R: Lactic acidosis with phenformin therapy. Calif Med 117:14-19, Jul 1972

Lactic Acidosis with Phenformin Therapy

THAYER CLEAVER, M.D., and ROBERT CARRETTA, M.D., *Stockton*

■ *Nine cases of severe acidosis occurring in patients with maturity onset diabetes who were receiving phenformin therapy were reviewed. All had evidence of renal disease. Lactic acidosis was diagnosed by elevated blood lactate levels in seven patients, and by the clinical manifestations and laboratory information in the other two. Contributing factors are discussed, as well as means of treatment and prevention. Although the specific etiology of renal disease is not emphasized in this paper, unrecognized progressive deterioration of renal function is implicated in the etiology of lactic acidosis.*

INCREASED BLOOD LACTIC ACID levels associated with phenformin (N'-betaphenethylbiguanide) therapy have been described since the introduction of the drug. A profound state of metabolic acidosis associated with a striking elevation of lactic acid has long been recognized as a potential hazard in its use.[1,2,3,4] The general subject of lactic acid acidosis was excellently reviewed recently,[5] and there appear to be multiple causes contributing to the condition. Phenformin therapy in diabetic patients and evidence of underlying renal disease, two of these etiologic factors, were present in nine cases of lactic acidosis recently recognized at the San Joaquin General Hospital. Five of these cases are presented because of the widespread use of phenformin in maturity onset diabetes and to support a recommendation that phenformin be included in the general reevaluation of the role of oral hypoglycemic agents in diabetes.

Case 1. A 51-year-old white man was admitted with a history of two days of nausea, vomiting, abdominal pain and progressive shortness of breath. Three years earlier, an anterior and posterior resection had been performed for adenocarcinoma of the rectum. He had been in hospital a month previously with obstructive nephropathy thought to be due to benign prostatic hypertrophy. Three days before admission, nitrofurantoin had been started for a urinary tract infection. Medications were digoxin 0.25 mg a day and phenformin 50 mg capsules (DBI-TD®) twice daily, which he had taken for five months since discovery of adult onset diabetes mellitus.

The patient was lean, weak, oriented and dyspneic. Blood pressure was 165/75 mm of mercury and respiratory rate 32 per minute. Surgical scarring compatible with the history was present on the abdomen, mild AV nicking was noted in the optic fundi, and the patient was pale. There were no other significant abnormalities.

Laboratory results included blood sugar of 150 mg per 100 ml, hematocrit of 31 percent and creatinine of 6.0 mg per 100 ml. The venous pH was 6.93, the pCO_2 23 mm of mercury, potassium 6.7 mEq per liter and plasma bicarbonate 5 mEq with a base deficit of 24 mEq. Sodium was 139 mEq per liter and chloride 98 mEq. A presumptive diagnosis of lactic acidosis was made and four liters of fluid with 360 mEq of sodium bicarbonate* were given in the next

From the Department of Medicine, San Joaquin General Hospital, Stockton.

Dr. Carretta now with U.S.A.F. (M.C.), Richards Gebaur AFB, Missouri.

Submitted, revised, September 15, 1971 (Addenda April 26, 1972).

Reprint requests to: T. Cleaver, M.D., San Joaquin General Hospital, P.O. Box 1020, Stockton, Ca. 95201.

*The bicarbonate requirement in mEq, to be found in standard textbooks, may be rapidly calculated as follows by use of an arterial blood gas determination: the "base deficit" in milliequivalents per liter is simply multiplied by the "bicarbonate space" in liters. The latter figure is roughly 45 percent of the body weight in kilograms for both adults and children (one liter weighs one kilogram). Thus, sodium bicarbonate required for a 70-kilogram patient with a base deficit of 20 milliequivalents per liter would be derived as follows: $NaHCO_3$ required = 0.5x70 kg × 20 mEq/L = 700 mEq. Any overestimate inherent in this method is overshadowed by the urgency of the clinical situation and the need for continued blood gas monitoring.

24 hours, two-thirds of it in the first six hours. The creatinine was 4.1 mg per 100 ml by this time, with creatinine clearance of 15 ml per minute and the blood urea nitrogen was 96 mg per 100 ml. The lactic acid level before institution of therapy was 173 mg per 100 ml (normal levels of 5 to 20 mg, BioScience Laboratories).

The subsequent hospital course was uneventful. Values for SGOT, SLDH, and SCPK were normal throughout.

Case 2. The patient was a 63-year-old Mexican-American woman with a history of diabetes mellitus for 25 years, easily controlled by 30 units of NPH insulin a day. Urinalysis on several occasions over a two-year period showed 2+ proteinuria, with urine pH averaging 5.5. Because of her obesity and relatively low insulin requirement, an attempt was made to control hyperglycemia with one phenformin capsule three times a day. This was successful, as judged by the clinical appearance and the blood sugar determination, and insulin was discontinued. The blood sugar remained satisfactory, and the patient did well for two months, when she began having mild diarrhea associated with abdominal pain, vomiting and lethargy.

On examination, the patient was observed to be acutely ill, diaphoretic, obese, oriented and eupneic, with respirations 22 per minute and a blood pressure of 80/60 mm of mercury. The rectal temperature was 36.4°C (97.6°F), the pulse 75 and regular.

Laboratory data on admission showed blood sugar of 273 mg per 100 ml and serum acetone reactive at 1:2 dilution. The arterial pH was 6.80, the pCO_2 15 mm of mercury, the plasma bicarbonate undetectable, and the base deficit 32 mEq per liter. The potassium was 6.6 mEq, sodium was 137 mEq, the chloride was 87 mEq per liter. The blood cell count was not remarkable except for hematocrit of 33 percent. Normal values for SGOT, SLDH, SCPK, and amylase were obtained.

A presumptive diagnosis of lactic acidosis was made, but unfortunately a blood specimen for lactate and pyruvate was lost. The bicarbonate required to correct the serum acidosis was rapidly calculated, and 160 milliequivalents of $Na\,HCO_3$ was given with two liters of 5 percent dextrose in one half normal saline solution as fast as possible.

An x-ray film of the chest showed passive pulmonary congestion, and digitalization was begun. The patient was given 40 units of regular insulin intravenously and subcutaneously. Antibiotic therapy for pyuria was begun.

Twelve hours later, the acidosis was corrected and the patient had received 8 liters of fluid, 80 units of regular insulin, and 850 mEq of sodium bicarbonate. At this time, the pH was 7.56, the plasma bicarbonate 24 mEq per liter, the pCO_2 40 mm of mercury and the potassium 3.2 mEq per liter. Serum acetone was positive undiluted; blood sugar was 185 mg per 100 ml. Eight hours later, the urine became alkaline and large amounts of acetone appeared in it. Serum creatinine of 2.6 per 100 ml with a creatinine clearance of 33 ml per minute was subsequently demonstrated. The hospital course thereafter was uneventful and the patient was discharged with prescription of 40 units of NPH insulin daily.

Case 3. The patient was a 49-year-old black woman with diabetes of three years' standing that was controlled with phenformin 50 mg capsules and diabinese 250 mg, each three times a day. For three days before admission she had progressive shortness of breath. Serum creatinine was 1.6 mg per 100 ml and creatinine clearance was 41 ml per minute.

On physical examination the patient was observed to be disoriented and obese. Blood pressure was 100/60 mm of mercury, deep respirations were 40 per minute and the rectal temperature was 37°C (96.8° F). The pulse was 100 a minute. The neck veins were distended with the patient sitting at 30 degrees, and rales were present at the left posterior lung base. There was a grade II aortic systolic murmur.

Laboratory studies of significance included blood sugar of 48 mg per 100 ml, negative serum acetone, pCO_2 of 15 mm of mercury, arterial pH of 6.98 and potassium of 6.0 mEq per liter. The plasma bicarbonate was 4.5 mEq per liter with a base deficit of 22 mEq per liter. Sodium was 136 mEq and chloride 105 mEq per liter. Normal values for SGOT, SLDH, SCPK, and amylase were obtained. The hematocrit was 35 percent. The lactate-pyruvate determination was 153 mg/3.5 mg per 100 ml (normals 5 to 20/0.3 to 0.9, Bio-Science Laboratories).

Treatment during the first four hours included administration of 2 liters of fluid and 570 milliequivalents of sodium bicarbonate. As the central

venous pressure rose, the blood pressure fell. Digitalis, furosemide, and isoproterenol drip were initiated. By this time the blood sugar was 173 mg per 100 ml, the pH 7.22, the pCO_2 22 mm of mercury, the plasma bicarbonate 9 mEq per liter and the base deficit 18 mEq per liter. Urine sugar and acetone determinations were negative. Nine hours after admission, the patient had received 1,220 milliequivalents of sodium bicarbonate with 4.5 liters of fluid, and the central venous pressure had begun to decline. In spite of this apparent improvement, the pH dropped to 7.00. Shortly thereafter, she died. Nephrosclerosis and passive congestion of the liver were found at autopsy. Pneumonitis was not present.

Case 4. An 80-year-old white man was admitted, without subjective complaints, because of cardiac arrhythmia. He was taking digoxin 0.25 mg a day, phenformin 50 mg capsules twice a day, tolbutamide 500 mg four times a day, reserpine 0.25 mg twice a day and Dyazide® once daily.

The pulse was irregular, averaging 80 beats a minute, blood pressure 180/90 mm of mercury, and respirations quiet at 20 per minute. Grade II atherosclerotic changes were present in the optic fundi, a grade III aortic ejection murmur was heard, and a large amount of pitting ankle edema was present. The hematocrit was 37 percent, blood sugar was 110 mg and BUN 26 mg per 100 ml, plasma bicarbonate was 19 mEq per liter and the electrolytes were normal. There were 15 to 20 hyaline casts per field in the urinary sediment.

Phenformin and tolbutamide were continued, digoxin was discontinued, and the arrhythmia was treated with lidocaine and propranolol. The creatinine was found to be 1.4 mg per 100 ml and the creatinine clearance was 71 ml per minute. The patient was cautiously redigitalized with 0.125 mg digoxin daily, beginning the seventh hospital day. Blood sugar at this time was 66 mg per 100 ml. Five hours later, the patient became restless, although the vital signs remained stable, including eupnea at a rate of 24 per minute. The urine sugar and acetone determinations were negative, and the urinary output was satisfactory. Laboratory values included arterial pH of 6.80, pCO_2 less than 4 mm of mercury, plasma bicarbonate of 5 mEq per liter and a base deficit of 22 mEq per liter. Serum potassium was 6.5 mEq per liter. The SGOT and SCPK were normal. A repeat blood sugar determination was 168 mg per 100 ml and creatinine 5.6 mg per 100 ml. The patient died before appropriate therapy was begun. Nephrosclerosis and nodular prostatic hyperplasia were found at autopsy. No serum lactate level was obtained.

Case 5. A 67-year-old senile white woman presented with lethargy and disorientation of five hours' duration and nausea and vomiting for one day. The only other illness known was hypertension, for which she received phenobarbital, 30 mg three times a day, chlorhydrothiazide 500 mg daily, alphamethyldopa 250 mg twice a day, reserpine 0.25 mg twice a day and potassium chloride 1 teaspoon twice a day. Additionally she took chlorpromazine 25 mg at four-hour intervals as needed, and had taken phenformin 50 mg twice a day for six years. She had been in hospital five months before this admission for an exacerbation of abdominal pain of two years' duration. Upper and lower gastrointestinal series, liver enzymes, and amylase were all normal at that time, and no diagnosis was reached.

On examination, the patient was noted to be lethargic, disoriented and obese. Blood pressure was 120/60 mm of mercury, respirations 28 per minute, pulse rate 70 and regular, temperature 35°C (95°F) rectally. She was pale, had moderate ankle edema, and rales at both lung bases. There were no localizing neurologic signs.

Urinalysis showed large acetone content and 2+ protein. The hematocrit was 33 percent, blood sugar 135 mg per 100 ml without acetonemia. An arterial blood pH was 6.84, plasma bicarbonate 3 mEq per liter, pCO_2 26 mm of mercury, with a base deficit of 22 mEq per liter, potassium was 4.3 mEq and sodium 147 mEq per liter. At this point, lactic acidosis was diagnosed. Central venous pressure was 11 cm of water. In the next 90 minutes 400 mEq of sodium bicarbonate was given, bringing the arterial pH to 7.24, with the plasma bicarbonate 8 mEq per liter and the remaining base deficit 19. After administration of 578 mEq of bicarbonate in the next five hours, pH was 7.27, plasma bicarbonate 5 mEq and base deficit 14 mEq per liter.

Although the central venous pressure was stable, the sodium content was 158 mEq per liter by this time, and the potassium 4.6 mEq. The patient had received a total of 25 units of regular insulin, as the blood sugar had climbed to 153 mg per 100 ml, and 320 mEq of potassium

chloride in 4 liters of one-fourth normal saline solution. In addition, she had been digitalized and had a good urinary output.

Since it was apparent that the patient had reached a critical point between salt overload and lack of complete response to alkali, tromethamine was tried, intravenously. She required no subsequent bicarbonate, and within three hours the pH was 7.37 and plasma bicarbonate 14 mEq per liter. Seventeen hours after admission, the pH was 7.51 and the plasma bicarbonate 35. Twenty-four hours after admission, the pH was 7.40. The serum creatinine was 2.1 mg per 100 ml and blood urea nitrogen 28 mg per ml. During the first three hospital days, these maximum enzyme levels were reached: SLDH 696, SGOT 500, SGPT 40, SCPK 504. Several serum amylase determinations were normal. Serial electrocardiograms revealed old anteroseptal myocardial infarction and nonspecific ST-T wave changes which persisted throughout the hospital stay, which was subsequently uneventful. The creatinine stabilized at 1.8 mg per 100 ml. Serum lactate was 308 mg and pyruvate 3.1 mg per 100 ml.

Four additional cases are summarized in Table 1.

Discussion

Phenformin is thought to inhibit oxidate metabolism at the cellular level and to increase anaerobic metabolism with a resultant increase in lactic acid production.[3,4] Excretion of the drug is decreased with renal dysfunction. Lactic acidosis as a distinctive and potentially lethal syndrome is known to be a risk with high doses of phenformin, or with excessive retention of low doses. Small rises in blood lactic acid levels may be found with phenformin doses only slightly above the recommended maximum of 150 ml per day.[1] Thus, it would appear that since excretion of phenformin is via the kidneys, decreased renal function may cause excessive retention of the drug, which in turn may increase the anoxic proportion of cellular metabolism.

Other causes of tissue anoxia may accelerate the process, especially shock of any cause.[4] Additional frequently found factors are ethanol consumption, infection—especially pyelonephritis—and uncontrolled diabetes mellitus. The syndrome is occasionally seen in leukemia and in type I glycogen storage disease. It has also occurred without known cause.

Recognition of the syndrome of lactic acidosis in diabetic patients requires an awareness of the above factors in a patient with a severe metabolic acidosis out of proportion to the blood glucose and acetone levels. The urine sugar and acetone are usually absent to moderately elevated, although they may be up sharply. The blood lactate level is elevated and the pH is depressed, usually profoundly by the time the disease is recognized.

It can be appreciated from the foregoing that the toxic effect of excessive phenformin levels, presumably anoxic metabolism, can be coupled with that of shock of any cause, particularly in the face of the increased oxygen demands of infection. In such circumstances, as shock begets shock, the shock of lactic acidosis becomes an autoaccelerating phenomenon.

Treatment, because of the truly emergency nature of the illness, must be prompt and aggressive; yet, even so, the prognosis is poor. The basic principles remain:

1. Correct the underlying cause, withdrawing phenformin.

2. Correct any causes of anoxia or shock, such as acidosis, hypovolemia, sepsis, diabetic ketoacidosis, pain, hypoglycemia, severe anemia, or correctable causes of renal failure.

In the cases presented, phenformin was discontinued; the shock was treated with blood volume expansion by intravenous fluids, and a large proportion of the calculated base deficit was given rapidly. We prefer an intravenous administration of 60 to 100 percent of the bicarbonate requirement in one to six hours. Requirements for insulin can be judged principally by blood sugar, and acetone, as is usual with uncomplicated diabetic ketoacidosis.

Dialysis may become a most important therapeutic regimen in patients who cannot tolerate large sodium or fluid loads. It may be hypothesized that bicarbonate buffering would be of greater benefit than acetate or lactate buffering, although this does not presuppose that excess lactate ion is in itself toxic. However, since the pyruvate-lactate equilibrium is in favor of lactate, and the latter must be metabolized to bicarbonate via pyruvate to act as a buffer, lactate is an inefficient buffer in this disease. This should be an early consideration if hemodialysis is unavailable. However, use of this drug is controversial.[8,9]

Table 1.—*Patient Characteristics*

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Age, Sex	51 M	63 F	49 F	80 M	67 F	54 F	72 F	63 F	70 M
Symptoms,									
Cerebral		lethargic	disoriented		lethargic, disoriented		confused	confused	
Abdominal	pain, nausea, vomiting	pain, diarrhea vomiting		diarrhea	vomiting		nausea	nausea, pain	
Other	dyspnea		dyspnea			dyspnea			
Phenformin 50 mg	bid	tid	tid	bid	bid	bid	qid	bid	bid
Creatinine (mg per 100 ml)	6.0	2.6	1.6	5.6	2.1	3.7	2.5	2.7	1.5
Urinalysis	normal	protein++ WBC 15	normal	normal	acetone-large, protein++	normal	acetone-small, WBC few, protein++	acetone-small	WBC 6-8
Other evidence of renal disease	obstructive nephropathy pyelo-nephritis						pyelo-nephritis	urethral stricture	
Evidence of liver disease						alcoholic			alcoholic
Evidence of vascular disease other than diabetes mellitus	✔		✔	✔	✔	✔	✔	✔, pacemaker	✔
Blood pressure	165/75	80/60	100/60	180/90	120/60		120/70	60/40	138/70
Blood sugar/acetone	150/0	123/1:2	48/0	66/0	135/0	251/small	270/0	78/trace	28/0
Packed red cell volume %	31	33	35	37	33	38	31	32	37
pH*	6.93	6.80	6.98	6.80	6.84	6.85	7.07	7.14	7.03
Bicarbonate mEq/L	5	0	4.5	5.0	3	8	8	9	7.5
Therapy-liters	4	8	4.5		4		4	7	5
Bicarbonate mEq/L	360	850	1220		978		792	704	440
Tromethamine					✔		✔		
Lactate/Pyruvate, mg per 100 ml	173/–	–	153/3.5	–	308/3.1	120/1.7	127/3.8	285/3.5	178/4.5

*Arterial in all but Case 1.

Tromethamine may offer an acceptable alternative to huge loads of sodium bicarbonate, especially with extreme pH depression, or in patients with significant cardiac disease.

The patients presented had as a common denominator phenformin therapy for diabetes in doses of 100 or 150 mg per day, and probable renal disease. Mild anemia was present in all cases. Symptoms of abdominal pain experienced by Cases 1, 2, 5 and 8 could be explained by uncontrolled diabetes mellitus or a side effect of phenformin, although pancreatitis has been described as a common complication of lactic acidosis.[6] The diarrhea seen in Cases 2 and 4 and vomiting and nausea in Cases 1, 2, 5, 7 and 8 may be due to the same cause, although digoxin toxicity may have contributed in Case 4. Cases 2, 3, 5, 6, 7 and 8 were mildly to moderately hypothermic before fluid therapy, and the patients in Cases 3, 4, 5, 7 and 8 experienced altered consciousness.

Shortness of breath was prominent in Cases 1, 2 and 4. Although the patient in Case 1 was under treatment with nitrofurantoin, no pulmonary infiltration was apparent on chest roentgenograms. We have no explanation of why there was no hyperpnea or tachypnea in Cases 2, 4, 5 and 8.

The rather low blood sugar obtained early in the course of Case 3 may have been due to excessive retention of chlorpropamide as well as phenformin, on the basis of chronic renal disease. Only phenformin is likely to have accounted for this in Cases 4, 8 and 9. It is evident that low blood sugar has no general predictive value in reference to the onset of lactic acidosis.

Enzyme elevations may be obtained in shock without implication of other underlying cause. However, as in severe diabetic ketoacidosis, the authors recommend a routine electrocardiogram on the third hospital day of lactic acidosis therapy. Clinical myocardial infarction did not develop in any of the nine cases, although the patient in Case 5 was watched with special care.

The unifying factor in each case was decreased renal function. Certainly, none of the patients presented had "a uremic picture." However, it is well recognized that 50 percent renal nephron destruction may occur before a significant rise in blood urea nitrogen or creatinine appears. More subtle signs were available, such as the 2 plus proteinuria of Case 2 or the creatinine clearance of 71 ml per minute in Case 4. The presence of artherosclerotic disease with increasing age, coupled with the potential of Kimmelstiel-Wilson disease in any patient with diabetes forces the conclusion that decreasing renal function is to be expected in any diabetic. An additional misleading facet is that of marginal renal function, which may drop sharply under stress yet speedily return to previous levels without significant additional loss of nephrons.[7] The problem, then, is anticipating the stresses, some of which have been discussed above, and defining the meaning of the word *marginal.*

Since it is well known that the serum creatinine and blood urea nitrogen do not reflect subtle renal disease, we are currently using 90 ml per min as a minimum creatinine clearance before prescribing phenformin, since in our experience significant retention of the drug may occur below this level.

Gradual deterioration of renal function or any acute intercurrent illness causing depression of renal function can result in the occurrence of lactic acidosis in patients who apparently have tolerated phenformin therapy for some time. This drug should certainly never be given in presence of elevated blood urea nitrogen or creatinine, and creatinine clearance should be determined in all other patients before selecting it as the drug of choice. The physician must choose candidates for phenformin therapy with considerable discretion and then be constantly alert to complications.

TRADE AND GENERIC NAMES OF DRUGS

DBI-TD® ..... *phenformin*
Orinase® ..... *tolbutamine*
Dyazide® ..... *triamterine with hydrochlorothiazide*
Diabinese® ..... *chlorpropamide*
Hydrodiuril® ..... *hydrochlorothiazide*
Aldomet® ..... *alphamethyldopa*
Thorazine® ..... *chlorpromazine*
Tham-E® ..... *tromethamine*

REFERENCES

1. Gottlieb A, Duberstein G, Geller A: Phenformin acidosis. N Engl J of Med 267:806-809, Oct 1962
2. Tranquada RE, Bernstein S, Martin HE: Irreversible lactic acid acidosis associated with phenformin. JAMA 184:37-42, Apr 1963
3. Young JM, Armanino P: Lactic acidosis and phenformin intoxication. Calif Med 103:198-202, Sep 1965
4. Bermer GM, Miller M, Springate GS: Lactic acidosis and phenformin. JAMA 184:43-46, Apr 1963
5. Oliva TD: Lactic acidosis. Am J Med 48:209-225, Feb 1970
6. Tranquada RE, Grant WJ, Peterson CR: Lactic acidosis. Arch Intern Med 117:192-202, Feb 1966
7. Beck AD: Benign prostatic hypertrophy and uraemia. Br J Surg 57:561-565, Sept 1970
8. Bleich HL, Schwartz WB: Tris Buffer (Tham). N Engl J Med 274:782-787, Apr 1966
9. Nahas GG: Letter. N Engl J Med 275:1203-1204, Nov 1966